REMARKS

Claims 11-12, 31-33, 50-51, and 61 are pending in the above-identified application, claims 1-10, 13-30, 34-49, 52-60, and 62-82 having been cancelled by this amendment without prejudice to applicants. Accordingly, claims 11-12, 31-33, 50-51, and 61 remain for consideration.

Claims 1-10, 13-30, 34-49, 52-60, and 62-82 were cancelled pursuant to a restriction requirement made final. This cancellation is without prejudice to the filing of a properly copending divisional, continuation, or continuation-in-part application directed to the subject matter of some or all of these claims.

Claims 11-12, 31-33, 50-51, and 61 were rejected under the first paragraph of 35 U.S.C. § 112 as based on a specification lacking enablement for the claims.

Reexamination of the application as amended, reconsideration of the rejection, and allowance of the claims remaining for consideration are respectfully requested.

The three-month shortened statutory period for response expires on February 6, 2002. Accordingly, this response is being filed in a timely manner.

I. THE REJECTION UNDER THE FIRST PARAGRAPH OF 35 U.S.C. § 112.

Claims 11-12, 31-33, 50-51 and 61 were rejected under the first paragraph of 35 U.S.C. § 112 for lack of enablement. This rejection is respectfully traversed.

It was stated that the specification was inadequate to enable one of ordinary skill in the art to produce a monoclonal antibody having the specific characteristics recited in

claim 11, namely, specific affinity and cross-reactivity limitations. This rejection is respectfully traversed, because sufficient enablement exists to meet the legal standard required by the first paragraph of 35 U.S.C. § 112 and the governing case law.

To summarize briefly, Example 1 describes the preparation of carbon-22 substituted derivatives of tacrolimus. Example 2 describes the preparation of a tacrolimus-keyhole limpet hemocyanine conjugate. The preparation of monoclonal antibodies to tacrolimus using the tacrolimus conjugate with keyhole limpet hemocyanin is described in Example 5. The immunization schedule and immunogens used, including the adjuvants, are described. The fusion was performed by standard method using a non-secreting murine myeloma. The screening procedure is described in detail and a monoclonal antibody having these characteristics was isolated and described. This is recited in detail in the specification at pages 29-31.

The rejection is respectfully traversed on the following grounds:

Firstly, the burden of the Patent and Trademark Office to show nonenablement has not been met. As a matter of Patent Office practice, the specification must be taken as in compliance with the first paragraph of 35 U.S.C. § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support. In re Marzocchi, 169 U.S.P.Q. 367 (C.C.P.A. 1971). Moreover, properly reasoned and supported statements explaining any failure to comply with the enablement requirement of § 112 are a requirement to support such a rejection. In re Wright, 27 U.S.P.Q. 2d 1510 (Fed. Cir. 1993).

The Office Action has provided no evidence of reasoning whatsoever that would support a conclusion of lack of enablement or undue experimentation of these claims. There is absolutely no suggestion, for example, that the derivatization and coupling process with tacrolimus would not work as described, that polyclonal antibodies could not be produced by immunization using adjuvants as described, that the fusion process using a standard non-

secreting fusion partner would not work, or that the screening process would not work. In fact, there is no objective or empirical basis whatsoever for a conclusion of nonenablement.

The Office Action has laid great stress on the fact that only one monoclonal antibody having the required characteristics was recited in the specification. Applicants would like to respectfully remind the Patent and Trademark Office that there is no requirement for even a single working example even in allegedly unpredictable technology, such as immunochemistry. In re Strahilevitz, 212 U.S.P.Q. 561 (C.C.P.A. 1982).

A certain amount of routine experimentation associated with the optimization of the Kohler-Milstein monoclonal antibody production process does not constitute undue experimentation. It is well recognized that a certain amount of routine repetition is required for monoclonal antibody production by cell fusion according to this process and that all attempts to produce monoclonal antibodies do not necessarily succeed. Such a degree of repetition and routine experimentation does not constitute undue experimentation in this technology. Johns Hopkins University v. CellPro, Inc., 47 U.S.P.Q. 2d 1705 (Fed. Cir. 1998).

The degree of unpredictability must be considered in the context of the invention and the knowledge of those skilled in the art. Even broad claims can be enabled if the subject matter of the claims is such that the unpredictability of the subject matter of the claims is minimized. See In re Vaeck, 20 U.S.P.Q. 2d 1438, 1444-45 (Fed. Cir. 1991) (claims directed to expression of chimeric genes in specific genera of cyanobacteria allowable even though claims not limited to expression of genes encoding particular *Bacillus* proteins in view of extensive understanding in the prior art of toxicity of *Bacillus* proteins).

All that is required to provide enablement is that any mode of making and using the invention be recited in the specification. Engel Industries, Inc. v. Lockformer Corp., 20 U.S.P.Q. 2d 1300 (Fed. Cir. 1991). This standard is clearly met here by the working example described above.

A review of the factors set forth by the Federal Circuit in In re Wands, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988) is useful. These factors are: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. Id.

A review of these factors indicates that enablement is present and there is no basis for a rejection on the grounds of lack of enablement under the first paragraph of 35 U.S.C. § 112.

The quantity of experimentation required is not excessive in view of the subject matter and the known properties of the Kohler-Milstein process for the production of monoclonal antibodies. Johns Hopkins University, 47 U.S.P.Q. 2d at 1705.

The amount of direction or guidance presented in the specification is substantial. Exact details are presented for the preparation of the immunogen, including the method of making the derivative of tacrolimus and the coupling of the tacrolimus to a suitable carrier. Additionally, details are presented on the screening of the monoclonal antibodies produced. A working example is present. The monoclonal antibody 1H6 is described. This monoclonal antibody was produced according to the methods recited in the specification and meets the claim limitations.

The nature of the invention is such that undue experimentation is not present. The claimed invention, from the standpoint of enablement, is a relatively restricted scope. The antibody binds a specific antigen and not a possible range of antigens. Moreover, the functional language recited in the claims in terms of affinity and cross-reactivity must be taken into account in evaluating the existence of enablement. In re Halleck, 170 U.S. 647 (C.C.P.A. 1970)

The state of the prior art suggests that what experimentation would be required is routine. Although the prior art here is not relevant with respect to the patentability of the invention, it does suggest that the Kohler-Milstein technique for preparing monoclonal antibodies by cell fusion is well understood and whatever experimentation is required is routine. Johns Hopkins University, 47 U.S.P.Q. 2d at 1705.

The relative skill of those in the art is relatively high. This invention is directed to Ph.D. biochemists or immunochemists or M.D.'s with extensive research experience. These individuals are well-versed in the relevant technology and know-how to perform such procedures.

The predictability or unpredictability of the art does not lead to a conclusion of nonenablement. The limited degree of unpredictability of the Kohler-Milstein process for the production of monoclonal antibodies does, as emphasized above, not lead to a conclusion that these claims are not enabled. There is simply no basis for such a conclusion in view of the specification and the presence of a working example.

The breadth of the claims strongly argues against lack of enablement. The claims are directed to monoclonal antibodies that bind a single, specific antigen with defined limits as to affinity and cross-reactivity. These monoclonal antibodies do not bind a range of antigens or analogues of the antigen. They bind a specific antigen. Moreover, the functional language in the claims and terms of the cross-reactivity and affinity must be taken into account in determining the scope of the claims and the existence of enablement. In re Halleck, 170 U.S.P.Q. at 647. These are not claims in which a degree of extrapolation is required such that would lead to undue experimentation. Compare In re Strahilevitz, 212 U.S.P.Q. 561 (C.C.P.A. 1982) with In re Fisher, 166 U.S.P.Q. 18 (C.C.P.A. 1970) (no enablement for claims to an ACTH preparation having a potency of at least 1 international unit/mg. when specification discloses preparation of ACTH of potency between 1.11 and 2.30 international units/mg). Here, the scope

of the protection sought is relatively circumscribed and the degree of experimentation required is minimal.

In fact, the Federal Circuit itself, in Wands, found that enablement existed and that undue experimentation was not present. It held that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 8 U.S.P.Q. 2d at 1404.

A careful review of the conclusions of In re Wands indicates that enablement is present, as was held in that case itself.

The Patent and Trademark Office training materials for examining patent applications with respect to enablement clearly state that a rejection for lack of enablement should not be made solely on the grounds that only one working example is present. "The presence of only one working example should never be the sole reason for making a scope rejection, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts in evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph – Enablement Chemical/Biotechnical Applications, *reprinted in* 2 Iver P. Cooper, *Biotechnology Law*, App. H-156, App. H-177 (2000).

What is in fact lacking in this rejection is an evaluation of all the facts in evidence and a statement as to why one would not be able to extrapolate that one example across the entire scope of the claims. The entire rejection is predicated on the existence of only one working example. That is legally insufficient according to Patent and Trademark Office policy and squarely contravenes the application of the factors of Wands.

Accordingly, this rejection is respectfully traversed and the Examiner is respectfully requested to withdraw this rejection.

II. CONCLUSION

In conclusion, all claims remaining for consideration are free of the prior art. These claims are fully enabled by the specification throughout their scope. Accordingly, prompt allowance of these claims is respectfully requested.

If a telephone call would be helpful in resolving any remaining issues, the Examiner is respectfully requested to telephone the undersigned at 310-788-5104.

Respectfully submitted,

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